The Rivers of Lethe and Mnemosyne Converge

Propofol and Memory Consolidation

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INCE its introduction in the 1980s, propofol has be
come the most widely used intravenous anesthetic in
clinical anesthesia. Its success is attributable to its pharma-
kinetic advantages and its versatile applications, including
the induction and maintenance of general anesthesia and
procedural and intensive care sedation. In addition to its
well-known sedative and hypnotic actions, propofol is a po-
tent amnestic agent, a desirable action in many of the un-
pleasant and stressful applications for its use. Modulation of
receptors for the inhibitory neurotransmitter γ-aminobuty-
ric acid is an important molecular mechanism for some of
the pharmacologic effects of propofol. Thus, knock-in mice
harboring γ-aminobutyric acid receptor type A β3 subunits
rendered insensitive to propofol or etomidate by a single
point mutation are resistant to the immobilizing effects of
propofol and etomidate in vivo.1 The molecular mechanism
for the amnestic actions of propofol has not been identified
directly, but a promising candidate is modulation of the α5
γ-aminobutyric acid receptor type A subunit. This subunit is
expressed in extrasynaptic γ-aminobutyric acid type A recep-
tors and is responsible for mediating tonic inhibitory cur-
rents in many neurons. Knockout of this receptor subunit in
mice eliminates the memory-blocking action of etomidate
without affecting sedation or hypnosis.2 Another potential
target that has been implicated in the amnestic actions of
propofol is the endocannabinoid system, a widespread para-
crine cell-signaling mechanism integral to several forms of
short- and long-term synaptic plasticity.3 Now comes a fas-
cinating study published this month in Anesthesiology4
showing that the endocannabinoid system indeed contrib-
utes to the effects of propofol on memory but counterintuitiv-
tely by enhancing retrograde memory consolidation rather
than suppressing anterograde memory, the better known ef-
effect of propofol on memory. This novel twist in the pharma-
ology of propofol suggests that a single drug blends the
most of the psychotropic effects of Δ2-tetrahydrocannabinol
(Δ2THC), the principal psychoactive component of canna-
bis. Propofol has been shown5 to inhibit the activity of fatty
acid amide hydrolase, a key enzyme in the degradation of
anandamide (fig. 1). Patel et al. reported that sedative doses
of propofol, but not of thiopental, increased brain concentra-
tions of anandamide in mice in vivo.5 Loss of righting
reflex, an index of hypnosis in mice, after administration of
propofol, but not thiopental, was antagonized by pretreat-
ment with the CB1 receptor antagonist rimonabant, whereas
pretreatment with WIN 55212-2, a CB1 receptor agonist,
potentiated loss of righting reflex caused by propofol. In
addition, propofol, but not thiopental, etomidate, or mida-
zolam, inhibited fatty acid amide hydrolase activity in vitro.
These findings implicated the endocannabinoid system in the
sedative actions of propofol, but not of the other intravenous
general anesthetics tested, through inhibition of the degradation
of endogenous CB1 receptor agonists such as anandamide.
Interaction with the endocannabinoid system by propofol is an
attractive candidate for some of the agent-specific actions of
propofol, compared with other general anesthetics, that are
shared with cannabinoids including its anxiolytic, mood alter-
ing, and postoperative dreaming effects.

Impaired learning and memory are well-known effects
of cannabinoids. These actions can be observed in animal
models of memory that depend on the hippocampus, a
brain region critical to various forms of memory and
known to express high concentrations of CB1 receptors.6
A role for the endocannabinoid system in anterograde
memory is supported by observations that cannabinoid
agonists impair, whereas antagonists or CB1 receptor
knock-down enhance, performance on hippocampal-de-
dendent memory tasks.7 However, recent studies dem-
strate that cannabinoids can facilitate memory consolidation
in specific situations, particularly in memory tasks
that involve an emotional component such as fear condi-
tioning.8 With this in mind, Hauer et al.4 tested the hy-
pothesis that propofol effects on endocannabinoid signaling
are involved in enhanced consolidation of emotionally
charged memories. Such an effect could be clinically rel-
EVANT to posttraumatic stress disorder after intraoperative
awareness or stressful intensive care unit events.

• This Editorial View accompanies the following article: Hauer D,
  Ratano P, Morena M, Scaccianoce S, Briegel I, Palmyer M,
  Cuomo V, Roozendaal B, Schelling G, Campolongo P: Propofol
  enhances memory formation via an interaction with the endo-
memory. Similar effects have been demonstrated when consolidation of short-term memory traces to long-term during encoding not by disrupting encoding but by prevent-
ging K⁺ channels. Anandamide is removed from the synapse by uptake into the postsynaptic neuron, where it is hydro-
lyzed and inactivated by fatty acid amide hydrolase (FAAH). Propofol indirectly activates endocannabinoid signaling by inhibiting FAAH, which increases intracellular anandamide concentration, reducing anandamide uptake and increasing synaptic anandamide concentrations. This increased concentration of synaptic anandamide activates presynaptic CB1 receptors, and reduces transmitter release. Propofol also inhibits postsynaptic neuronal activity through potentia-
tion of γ-aminobutyric acid_\textsubscript{A} (GABA_\textsubscript{A}) receptors.

In studies of human volunteers, treatment with low nonsedative doses of propofol to achieve a state of conscious amnesia during learning produces anterograde amnesia by impairing long-term memory consolidation. Thus, propofol disrupts memory formation when administered during encoding not by disrupting encoding but by preventing consolidation of short-term memory traces to long-term memory. Similar effects have been demonstrated when subanesthetic doses of propofol are administered during training in an aversive memory paradigm. Hauer et al. used a well-characterized animal model of aversive training, known as inhibitory avoidance, in which rats are trained to avoid a dark compartment associated with a foot shock. Memory retention was assessed 48 h later by measuring the time until the rat reentered the dark compartment (longer latency reflects stronger memory). Drug treatments at various times after the training period were used to determine their effects on memory consolidation, a paradigm that avoids drug effects on memory acquisition or encoding during training while detecting effects on posttraining consolidation. Relatively high anesthetic doses of propofol administered immediately or 30 min after training increased brain anandamide concentrations and enhanced retention of the aversive memory, whereas lower doses or administration of drug delayed 90 or 180 min after training had no effect. In contrast, anesthetic doses of midazolam or pentobarbital did not enhance retention of inhibitory avoidance or increase brain anandamide concentrations. Involvement of the cannabi
noid system was evident in the ability of a CB1 receptor antagonist (rimonabant) coadministered immediately after training to reduce the enhanced retention latency produced by propofol. Thus, propofol enhanced consolidation of aver-
sive memory in a time-sensitive manner involving CB1 recep-
tors and associated with increased brain anandamide. Ac-
tivation of the endocannabinoid system in the amygdala, a brain region that is important in aversive memory, is in-
volved in enhanced retention of inhibitory avoidance behavior. It will be interesting to determine whether the amygdala is also involved in propofol actions and whether propofol also affects consolidation in other nonaversive memory consolidation paradigms.

There are a number of important limitations to this study. The doses of propofol used are high for rat and so might not be relevant to typical doses encountered in clinical anesthesia or intensive care sedation. Rimonabant and other CB1 receptor antagonists have cognitive effects on their own, so it will be important to show that such parallel mechanisms are not involved in antagonizing the propofol memory deficit. Rimonabant has other off-target effects independent of CB1 receptors that should be ruled out as possible mechanisms. Other substrates for fatty acid amide hydrolase (such as oleylethanolamide) have procognitive effects independent of CB1 receptor agonism that could contribute to the propofol effect. Resolution of these questions should further focus the precise mechanism or reveal additional mecha-
nisms of propofol action. Finally, the story remains incom-
plete because other drugs known to inhibit fatty acid amide hydrolase, including some nonsteroidal antiinflammatory drugs, have minimal or no effects on memory. The reasons for this are unclear but might involve effects of cyclo-oxygen-
ase inhibition on endocannabinoid metabolism, for example. This question further reveals the complexities of endocan-
nabinoid signaling and memory mechanisms and highlights the need for additional investigations in this area.

The demonstration that propofol, but not a representa-
tive benzodiazepine or barbiturate, indirectly activates the endocannabinoid system to enhance aversive memory con-
solidation provides \textit{in vivo} evidence for a unique γ-aminobu-
tyric acid-independent mechanism of propofol action. That propofol has apparently agent-specific effects on the consol-
idation of aversive memories has potential clinical implica-
tions. It is plausible that this effect contributes to an in-

![Schematic representation of the propofol effect on endocannabinoid signaling at the synapse.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931117/)
creased incidence of aversive memories after intraoperative awareness associated with propofol-based intravenous anes-
thesia.\textsuperscript{15,16} In addition, the important role of the endocan-
nabinoid system in aversive memory consolidation provides a poten-
tial pharmacologic approach to blocking posttrau-
matic memory consolidation using CB\textsubscript{1} receptor antago-
nists. Although these hypotheses require further experi-
mental and clinical validation, it appears that propofol can no
longer be considered the “milk of amnesia” we remember.

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